PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 4 -32671A	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/10171	International filing date *(day/month/year)* 12.09.2003	Priority date *(day/month/year)* 13.09.2002
International Patent Classification (IPC) or both national classification and IPC C07D493/04		
Applicant NOVARTIS AG		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.03.2004	18.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Schmid, A Telephone No. +49 89 2399-8591

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/10171

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-38 as originally filed

Claims, Numbers

1-34 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 11-20,23-31,32

   because:

   ☒ the said international application, or the said claims Nos. 32 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 11-20,23-31

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees, the applicant has:

   ☐ restricted the claims.

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☒ the parts relating to claims Nos. 1-10,21,22,32-34 .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10,32,33
	No:	Claims	21,22,34
Inventive step (IS)	Yes:	Claims	
	No:	Claims	9,10,21,22,32-34
Industrial applicability (IA)	Yes:	Claims	1-10,21,22,33,34
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1) Claim 32 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV

Lack of unity of invention

1) The present subject-matter is considered to lack unity as already set out in the search report.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The preparation method according to present claims 1-8 differs from the closest prior art represented by WO-A-02 30356 in that the steps up to the compunds to be macrolactonized [compound 7] are quite different from the present ones. WO-A-02 30356 starts with an aldol condensation followed by macrolactonization whereas the present process uses various different steps including sulfonamide sulfonic esters to obtain such type of compounds.

   Accordingly the subject-matter of present claims 1-8 is novel pursuant to Article 33(2) PCT.

2) In view of the above prior art it was not predictable for a skilled person that the above process could be useful in order to produce epothilone derivatives easy in a good yield.

   Therefore the subject-matter of present claims 1-8 also involves an inventive step with regard to Article 33(3) PCT.

3) As regards present claims 9 and 10, the prior art does only disclose compounds with heteroaryl as substituent R_2 instead or aryl. Accordingly the subject-matter of present claims 9, 10 and related claims 32 and 33 are considered to be novel pursuant to Article 33(2) PCT.

Since heteroaryl substituents and "pure" aryl substituents are structurally not comparable it was not predictable that such compounds would in fact show the desired properties. However, since the applicant has not be proved the alleged properties, no inventive step can be acknowledged for present claims 9, 10, 32 and 33 with respect to Article 33(3) PCT.

4) D1: WO 2004/012735 A (BERGER MARKUS ;BOSSLET KLAUS (DE); KLAR ULRICH (DE); SCHERING AG () 12 February 2004 (2004-02-12) [intermediate document, the present priority has not been checked]
D2: WO 01/07439 A (MARTIN HARRY ;MULZER JOHANN (DE); SCHERING AG (US)) 1 February 2001 (2001-02-01)
D3: WO 99/54330 A (SQUIBB BRISTOL MYERS CO) 28 October 1999 (1999-10-28)
D4: HOEFLE G ET AL: "EPOTHILONE A-D AND THEIR THIAZOLE-MODIFIED ANALOGS AS NOVEL ANTICANCER AGENTS" PURE & APPLIED CHEMISTRY, PERGAMON PRESS, OXFORD, GB, vol. 71, no. 11, 1999, pages 2019-2024, XP001008755 ISSN: 0033-4545

disclose compounds (cf. search report) suitable for the production of epthilones which clearly fall under the scope of present claims 21 and 22.

Accordingly the subject-matter of present claims 21, 22 and 34 is not novel with regard to Article 33(2) PCT.

5) An inventive step step of the novel subject-matter is highly questionable since the disclosed compounds solve the same problem so that it was obvious for a skilled person to modify the known structures in order to obtain alternative compounds.

Therefore the novel subject-matter of present claims 21, 22 an 34 does not involve an inventive step with regard to Article 33(3) PCT.

6) For the assessment of the present claim 32 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The

patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII

Certain defects in the international application

1) WO-A-02 30356 and D1 to D4 which represents a relevant prior art should be referred to in the description in accordance to Rule 5(1)(a)(ii) PCT.